support throughout the Specification (*See e.g.,* the Examples) and are patentably distinct over the prior art cited in the presently pending Office Action.

Applicants note that the Patent Office continues to indicate an incorrect filing date for the present application. As indicated in the Request for Corrected Filing Date and Filing Receipt mailed November 24, 1999, Applicants request that the filing date be corrected in the record of the present case. A copy of the November 24, 1999, and its attachments is attached hereto at Tab 1, for the Examiner's convenience.

In the present Office Action, the Examiner has rejected the Claims under 25 U.S.C. §103(a), as allegedly being unpatentable under Yamamoto *et al.,* taken with Frazee *et al.* On page 3, of the Office Action, the Examiner states that Yamamoto *et al.* teach that leukotriene-B_4 and leukotrienes in general, play a role in the immunologic defense against microbial infection. The Examiner indicates that Yamamoto *et al.* teach that the intraperitoneal injection of LTB4 provides an increased survival rate of hosts infected with methicillin-resistant *Staphylococcus aureus*, by directly or indirectly regulating the immune system. In addition, the Examiner indicates that Yamamoto *et al.* teach that the peptide leukotriene-C_4 is involved in the immunologic response to infections. However, the Examiner admits that Yamamoto *et al.* do not teach administration of the leukotriene in an aerosol form.

The Examiner further indicates that Frazee *et al.* teach that it is well known in the art that leukotrienes (LTB4, LTC4, LTD4, and LTE4) are involved in pulmonary infection and disease. In addition, the Examiner indicates that Frazee *et al.* teaches the administration of a pharmaceutical at an organ site, as well as aerosolization of the pharmaceutical for inhalation. The Examiner argues that it " . . . would have been obvious to have modified Yamamoto *et al.* by using the teachings in Frazee *et al.*, which references when combined teach all of claims 22-26." (Office Action, page 3). Applicants must respectfully disagree.

Applicants assert that the Examiner has not met the burden of establishing a *prima facie* case of obviousness. A *prima facie* case of obviousness requires the Examiner to cite to a reference which (a) discloses all the elements of the claimed invention, (b) suggests or motivates one of skill in the art to combine or modify those elements to yield the claimed

combination, and (c) provides a reasonable expectation of success should the claimed combination be carried out.[1] Failure to establish **any one** of these three requirements precludes a finding of a *prima facie* case and, without more, entitles Applicant to allowance of the claims at issue.

Applicants must respectfully disagree with the Examiner's arguments regarding the Yamamoto *et al.* reference. In contrast to the Examiner's assertions, the Abstract makes no general statements regarding the role of leukotrienes in immunologic defenses against microbial infections. Rather, the Yamamoto *et al.* Abstract only indicates that "intraperitoneal administration of GCA and LTB_4 may play a role in host defense mechanism[s] during MRSA [methicillin-resistant *Staphylococcus aureus*] infection." Thus, there is no "general" teaching of the use of leukotrienes in immunologic defenses against microbial infections. Likewise, there is no indication that any administration route other than intraperitoneal injection is effective in enhancing the survival of animals following intravenous injection of MRSA. In addition, there is no indication that the leukotrienes administered intraperitoneally are effective against any organisms other than *Staphylococcus aureus*. Indeed, as indicated on page 528, the experiment described in this reference was "undertaken to see the influence of LTB_4 and GCA [ε-guanidino caproic acid methane sulfonate] on host resistance to challenge to intravenous challenge with a MRSA." Thus, there is no teaching in Yamamoto *et al.* of the antimicrobial solution of the presently claimed invention in which the suitable route of administration is something other than intraperitoneal (*e.g.,* aerosolization or intratracheal injection). Nonetheless, in order to further their business interests and the prosecution of the present application, Applicants have amended independent Claim 22 to recite that the solution is in a form suitable for aerosolization. Support for this amendment is found throughout the Specification as filed (*See e.g.,* Example 10). Applicants reserve the right to prosecute the originally filed (and/or similar) Claims in the future. New Claims 27-32 also finds support

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[1] *See, e.g., Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990); and *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

throughout the Specification (*See e.g.,* the Examples). Applicants submit that these new Claims are not rendered obvious by Yamamoto *et al.,* as there is no teaching nor suggestion in Yamamoto *et al.,* of the utility of the leukotriene-containing solution of the presently claimed invention against *Klebsiella pneumoniae*, nor is there any teaching or suggestion in Yamamoto *et al.,* of the utility of intratracheal administration of the leukotriene-containing solution of the presently claimed invention.

Applicants must also respectfully disagree with the Examiner's characterization of Frazee *et al.* In contrast to the implications made by the Examiner regarding the teachings of Frazee *et al.,* this reference teaches the use of leukotriene **antagonists** in the treatment of disease (*i.e.,* the compounds of Frazee *et al.* are administered in order to act *against* leukotrienes). Thus, Frazee *et al.* ***teaches away*** from the presently claimed invention, as according to the teachings of Frazee *et al.,* the administration of the leukotriene-containing solution of the present invention would be expected to cause or exacerbate disease. For example, as the Examiner indicates, Frazee *et al.* teach that "[l]eukotrienes have been implicated in a number of pulmonary diseases . . . . The presence of leukotrienes in the sputum of patients having cystic fibrosis, chronic bronchitis, and bronchiectasis at levels likely to have pathophysiological effects has been demonstrated . . . . Treatment of these diseases constitutes additional possible utility for leukotriene **antagonists**. (Frazee *et al.,* col. 1, line 65, through col. 2, line 16, *emphasis added*). Thus, there is absolutely no teaching in Frazee *et al.,* that the *administration* of leukotriene-containing solutions such as those presently claimed would have any beneficial effects in treatment of disease. Indeed, based on Frazee *et al.,* administration of leukotriene-containing solutions such as those presently claimed would have any detrimental effects and cause disease. As the Examiner must consider the teachings of Frazee *et al.* as a whole[2], there is absolutely no teaching that the leukotriene-containing

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[2] "Not only must the claimed invention as a whole be evaluated, but so also must the references, as a whole, so that their teachings are applied in the context of their significance to a technician at the time -- a technician without our knowledge of the solution." (*Interconnect Planning Corp. v. Feil*, 227 USPQ 543, 551, 774 F.2d 1132, 1143 (Fed. Cir. 1985).)

solution of the present invention is an antimicrobial or useful in the treatment of microbial infections. Applicants also submit that these new Claims are not rendered obvious by Frazee *et al.*, as there is no teaching nor suggestion in Frazee *et al.*, of the utility of the leukotriene-containing solution of the presently claimed invention against *Klebsiella pneumoniae*, nor is there any teaching or suggestion in Frazee *et al.*, of the utility of intratracheal administration of the leukotriene-containing solution of the presently claimed invention.

Thus, taken alone, neither Yamamoto *et al.*, nor Frazee *et al.* teach or suggest each and every element of the presently claimed invention. The combination of these references also fails to provide the remedy for this shortcoming of the references. Indeed, the combination of these references is nonsensical, in that Frazee *et al.* teach the deleterious effects of leukotrienes and the utility of leukotriene antagonists in the treatment of disease, while Yamamoto *et al.* discuss the intraperitoneal administration of leukotrienes to treat intravenously administered methicillin-resistant *S. aureus*. Thus, at most, the combination of these references *might* lead one of skill in the art to administer leukotrienes intraperitoneally to treat *S. aureus* bloodstream infections. There is ***no*** teaching in either of these references, taken alone or in combination, of the antimicrobial properties of the leukotriene solution as presently claimed, let alone in the formulations presently claimed. Likewise, these references, taken alone or in combination, provide no suggestion or motivation to one of skill in the art to combine or modify the elements described in these references. In addition, there is no reasonable expectation of success that the combination would result in the presently claimed invention.

In addition, Applicants assert that by suggesting that the combination of Yamamoto *et al.*, and Frazee *et al.* produces the presently claimed invention, the Examiner presents, in essence, an "obvious to experiment" or "obvious to try" standard for obviousness. The "obvious to try" standard has been thoroughly discredited. Indeed, an obviousness rejection is inappropriate, where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful" (quoting *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 [Fed. Cir. 1988], *Merck*

& Co., Inc. v. Biocraft Laboratories, Inc., 10 USPQ2d 1843, 1845 [Fed. Cir. 1989]). There is simply no guidance provided by either of these references that would lead one of ordinary skill in the art to produce the presently claimed invention, particularly in view of the fact that Yamamoto *et al.* **teach away** from the presently claimed invention.

As the Examiner has not set forth a *prima facie* case of obviousness, Applicants submit that the pending Claims are in condition for allowance and respectfully request that the rejections be withdrawn.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that Applicants' claims as amended should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect.

Dated: January 3, 2001

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